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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/416,579	10/12/1999	HANS-GEORG IHLENFELDT	BMID9967US	6338

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EXAMINER
PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
1652	27

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/416,579	Ihlenfeldt et al.
Examiner	**Art Unit**
Rebecca Prouty	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 3, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *15-58* is/are pending in the application.

4a) Of the above, claim(s) *22-53* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *15-21 and 54-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-13-03 has been entered.

Claims 1-14 have been canceled. Claims 15-53 and newly presented claims 54-58 are still at issue and are present for examination.

Claims 22-53 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 17.

Applicant is advised that should claims 18-20 be found allowable, claims 56-58 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See

MPEP § 706.03(k). Claims 56-58 are word-for-word identical to Claims 18-20. Did applicants intend Claims 56-58 to depend from Claim 54?

Claims 15-21 and 54-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 (upon which Claims 16-21 and 56-58 depend) is indefinite in the recitation of "hybridizing" as this term is unclear absent a statement of the conditions under which the hybridization reaction is preformed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions.

Claim 54 (upon which Claim 55 depends) is indefinite in the recitation of "*Drosophila melanogaster* gene coding for the native kinase" as *Drosophila melanogaster* encodes many kinases. The scope of the "native kinase" is unclear.

Claims 15-20 and 54-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Claims 15-20 and 56-58 are directed to a genus of deoxynucleoside kinases from any non-vertebrate organism (Claims 15, 17-20 and 56-58) or any insect (Claim 16) having a variety of recited characteristics. Claims 54 and 55 are drawn to any *Drosophila melanogaster* deoxynucleoside kinase which accepts all natural deoxynucleosides as substrates and is stable in the absence of SH reagents and stabilizing proteins. The specification teaches the structure of only a single representative species of such deoxynucleoside kinases (i.e., the *Drosophila melanogaster* Dnk encoded by SEQ ID NO:1). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality being a deoxynucleoside kinase for Claims 54 and 55. While Claims 15-20 additionally recite some specific characteristics of the claimed genera, these characteristics do not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. Given this lack of description of representative species encompassed by the

genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

While the primers recited in Claim 15 may not hybridize to other known deoxynucleoside kinase genes, these primers hybridize to only a very small fragment of any deoxynucleoside kinase gene and thus provide very little characterization of the protein encoded thereby. Furthermore, it should be noted that the claim does not recite the conditions under which the recited sequences must hybridize such that the scope of genes which would hybridize to these primers is wholly unclear.

Claims 15-20 and 54-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *Drosophila melanogaster* deoxynucleoside kinase encoded by SEQ ID NO:1, does not reasonably provide enablement for any non-vertebrate or any insect deoxynucleoside kinase with the claimed properties. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 15-20 and 56-58 are so broad as to encompass any non-vertebrate or any insect deoxynucleoside kinase which will hybridize to one or more of SEQ ID NOS:2-8 under undefined conditions while Claims 54 and 55 are so broad as to include any *Drosophila melanogaster* deoxynucleoside kinase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single deoxynucleoside kinase (i.e., the kinase of *Drosophila melanogaster* encoded by SEQ ID NO:1) with the claimed properties.

While recombinant and mutagenesis techniques are known, it is <u>not</u> routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and

the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all deoxynucleoside kinases of any non-vertebrate organism with the claimed properties because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting kinase activity and substrate specificity; (B) the general tolerance of deoxynucleoside kinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the

claimed invention in a manner reasonably correlated with the scope of the claims broadly including any deoxynucleoside kinases of any non-vertebrate organism with the claimed properties. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of deoxynucleoside kinases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-21 and 54-58 are rejected under 35 U.S.C. 102(a) as being anticipated by Johansson et al.

Johansson et al. teach the recombinant production of a *Drosophila melanogaster* deoxynucleoside kinase of 29 KD which phosphorylates all 4 natural deoxynucleosides as well as a number of nucleoside analogs. Johansson et al. disclose that this

enzyme has a specific activity of at least 20 U/mg and a specificity constant of $>10^4$ $M^{-1}s^{-1}$ for all four natural deoxynucleosides (see Table I). While the references do not teach the temperature optimum and stability properties of the enzyme, (Claims 15, 19 and 20) these are inherent characteristics of the protein.

Applicants state that the response included a statement by a translator of the German priority documents, but no such statement is present. Absent a translation of the priority documents, applicants claim to the benefit of the filing date of the previous applications can not be evaluated.

Claims 15-21 and 54-58 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Munch-Petersen et al., 1998 (Reference 11 of applicant's IDS) or Munch-Petersen et al., 1997 (Abstract P15 of Reference 5 of applicant's IDS).

Munch-Petersen et al., 1998 and Munch-Petersen et al., 1997 each disclose a *Drosophila melanogaster* deoxynucleoside kinase of about 30 KD which phosphorylates all 4 natural deoxynucleosides as well as a number of nucleoside analogs including ara-C and ara-T but lacking any kinase activity to AZT or dTMP. Munch-Petersen et al., 1998 disclose that this enzyme has a specific

activity of at least 20 U/mg and a specificity constant of $>10^4$ $M^{-1}s^{-1}$ for all four natural deoxynucleosides (see Table III) and a temperature optimum between 40°C and 60°C (page 3928). While the references do not teach the stability properties of the enzyme, (Claims 15 and 19) these are inherent characteristics of the protein.

The use of a 102/103 rejection for the rejection of a product-by-process claim has been approved by the courts. While the references do not specifically disclose the enzyme produced by recombinant production (as recited by the claims), the production of a protein by a particular process does not impart novelty or unobviousness to a protein when the same protein is taught by the prior art. This is particularly true when the properties of the protein are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 292-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562

F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Furthermore, even if applicants can show that the natural and recombinant proteins are different, it would have been obvious to one of ordinary skill in the art to produce this protein recombinantly. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. As such the disclosure of a useful protein, such as that of Munch-Petersen et al. clearly suggests to the ordinary skilled artisan the recombinant production of the protein in order to produce larger quantities of the protein. Therefore, it would have been obvious to one of ordinary skill in the art to isolate and express the gene encoding the kinase of Munch-Petersen et al. using well known recombinant methods for the isolation of the gene, insertion of the isolated gene into an expression vector, transformation into a suitable host and expression of the encoded protein.

Applicants argue that example 7 of the specification shows that the natural protein of the references and the recombinant protein of the specification differ in stability. However, this is not clear as the conditions for measuring stability used in this example are not presented. It appears that the assays were matched for the total number of units of enzyme used but there is no indication the recombinant and naturally isolated enzyme solutions were matched in total protein concentration. It is well known in the art that the total protein concentration of the enzyme solution used often has a large influence on the stability of an enzyme, and that recombinant solutions often have much larger total protein concentrations than corresponding solutions produced by purification from natural sources. This is in fact the reason BSA is often added to purified enzyme solutions. The fact that the stability of the natural enzyme is reported to be identical to that of the recombinant enzyme in Example 7 following the addition of 2.5 mg/ml of BSA to the natural protein suggests that the difference in stability reported in Example 7 is in fact not a real difference in the proteins themselves, but a difference in the total protein concentration between the two assays. One would expect that the two solutions would act identically if matched in total protein concentration (i.e., if

the natural enzyme solution was concentrated following purification, or the recombinant solution diluted with water).

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the

statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652